Preoperative endoscopic biliary drainage by metal versus plastic stents for resectable perihilar cholangiocarcinoma

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Background and Aims: Adequate preoperative biliary drainage (PBD) is recommended in most patients with resectable perihilar cholangiocarcinoma (pCCA). Most expert centers use endoscopic plastic stents rather than self-expandable metal stents (SEMSs). In the palliative setting, however, use of SEMSs has shown longer patency and superior survival. The aim of this retrospective study was to compare stent dysfunction of SEMSs versus plastic stents for PBD in resectable pCCA patients.

Methods: In this multicenter international retrospective cohort study, patients with potentially resectable pCCAs who underwent initial endoscopic PBD from 2010 to 2020 were included. Stent failure was a composite end point of cholangitis or reintervention due to adverse events or insufficient PBD. Other adverse events, surgical outcomes, and survival were recorded. Propensity score matching (PSM) was performed on several baseline characteristics.

Results: A total of 474 patients had successful stent placement, of whom 61 received SEMSs and 413 plastic stents. PSM (1:1) resulted in 2 groups of 59 patients each. Stent failure occurred significantly less in the SEMSs group (31% vs 64%; $P < .001$). Besides less cholangitis after SEMSs placement (15% vs 31%; $P = .012$), other PBD-related adverse events did not differ. The number of patients undergoing surgical resection was not significantly different (46% vs 49%; $P = .71$). Complete intraoperative SEMSs removal was successful and without adverse events in all patients.

Conclusions: Stent failure was lower in patients with SEMSs as PBD compared with plastic stents in patients with resectable pCCA. Removal during surgery was quite feasible. Surgical outcomes were similar. (Gastrointest Endosc 2024;99:566-76.)

(footnotes appear on last page of article)

Perihilar cholangiocarcinoma (pCCA) is the most common malignancy of the bile ducts and often results in obstructive jaundice.[1-3] Often, the only treatment option with curative intent is extensive surgical resection. Obstructive jaundice and especially cholangitis are established risk factors for adverse events after liver surgery.[4-6] To improve the future liver remnant (FLR) function and reduce the risk of postoperative liver failure, preoperative biliary drainage (PBD) with plastic stents (PS) placed by using ERCP is recommended if significant cholestasis is present.[6] However, drainage of pCCA is complex and frequently results in stent dysfunction characterized by episodes of recurrent jaundice and cholangitis, which may delay the time to surgery and increase the risk of postoperative infectious adverse events and subsequent liver failure.[7] Also PBD may be associated with higher postoperative morbidity compared with no PBD (RR, 1.266; 95% CI, 1.039-1.543), owing to increased infectious adverse events.[8] However, in patients with high bilirubin levels (>50 μmol/L), PBD seems necessary to minimize postoperative adverse events.

In the palliative setting, self-expandable metal stents (SEMSs) show superiority compared with PS regarding stent patency, adverse event rate, and need for reinterventions.[9] However, owing to historic expertise and cost constraints, most expert centers use PS for initial endoscopic PBD for resectable pCCA. Uncovered self-expandable metal stents (ucSEMS) are being placed only after confirmation of cancer, which can be challenging in patients with suspected pCCA. In addition, SEMSs may cause more tissue reaction and tumor overgrowth, making stent

removal during surgery more difficult. For resectable malignant distal biliary obstruction, the ESGE guidelines of 2012 already recommend SEMSs placement.[10]

Only a few studies have been published on the use of SEMSs for PBD in perihilar obstruction. Grunhagen et al.[11] demonstrated that SEMSs were superior to PS in patients with resectable pCCA, because of rapid and adequate biliary decompression, fewer reinterventions, lower cholangitis rate, and shorter median time to laparotomy. That study consisted of only 27 patients of whom 14 were treated with SEMSs. Ten patients underwent surgical resection with uneventful stent removal. Other studies on SEMSs removal for perihilar obstruction reported similar results.[12-14] Limitations of these studies were small number of patients, selection of patients only undergoing resection, lack of long-term adverse events or follow-up, and no direct comparison with patients who underwent PS placement as PBD.

Therefore, in this large multicenter international retrospective cohort study, we aimed to analyze stent failure of SEMSs versus PS in patients with potentially resectable pCCA needing PBD.

METHODS

Study design and study population

A multicenter international retrospective cohort study was performed at 4 tertiary referral centers for hepatobiliary diseases (Erasmus MC, Amsterdam UMC, Aintree University Hospital, and Innsbruck Medical University). All patients from January 2010 to December 2020 with potentially resectable pCCAs as determined at the multidisciplinary team meetings were eligible, regardless of whether they ultimately underwent surgery. Patients who underwent initial PBD with the use of ERCP, with or without successful stent placement, were included from prospective pCCA databases. The standard assessments for those patients included computed tomography and magnetic resonance imaging. Patients were excluded if initial PBD was done with a percutaneous approach, or if patients were deemed unresectable or inoperable at presentation. This study was conducted according to the guidelines in the Helsinki Declaration (MEC-2020-0500) and the STROBE guidelines. Ethical and institutional approvals were obtained at all participating centers.

ERCP procedure

Before ERCP, cross-sectional imaging (CT or MRCP) was performed in all patients. All ERCP procedures were performed with conscious sedation or general anesthesia/propofol administration. Prophylactic antibiotic therapy and nonsteroidal antiinflammatory drugs were administered to all patients according to local protocol. The procedures were performed either in a regional center before referral or in one of the 4 tertiary referral centers after informed consent for the ERCP was obtained. Sphincterotomy was frequently performed when a stent was placed and in other cases when deemed necessary by the endoscopist. If the pancreatic duct was cannulated with either contrast or wire, prophylactic pancreatic duct stenting was performed by choice of the endoscopist. The goal of PBD was to ensure drainage of the FLR as well as to ensure appropriate resolution of jaundice. This was done to target at least 50% of viable liver to be drained including the FLR. Decisions related to single or multiple stents were based on these principles and the patient's biliary anatomy at the time of ERCP by the endoscopist. Almost all stents were placed crossing the papilla. Whenever a sector was opacified during the ERCP, this was targeted for drainage to reduce infection risk. The number, length and diameter of the stent was at the discretion of the endoscopist. In the Aintree University Hospital, uncovered SEMSs were used from 2010 onward for these patients, and criteria for ucSEMS placement were similar to that for PS. Covered SEMSs placement criteria were similar for PS. A PS was placed at the same procedure as the SEMSs if the biliary anatomy precluded appropriate placement of the proximal end of the SEMSs, primarily because of blocking of segmental branches. In patients with a high suspicion of benign disease, PS were used. In the 3 centers other than Aintree University Hospital, mostly PS were used for PBD. Stents of different types, lengths, and diameter were used, mostly PS from Cook or Boston varying from 5 to 10 F in diameter and from 9 to 18 cm in length; or covered and uncovered SEMSs from Cook or Boston, 8-10 mm in diameter and 8-10 cm in length (all stent characteristics are presented in Appendix 1, available online at www.giejournal.org). Scheduled PS exchange was routinely performed at 3-month intervals. Before stent placement, pathologic proof in the form of cytologic brushes, intraductal biopsies, or cholangioscopy-guided biopsies were routinely obtained. Pathologic proof was not necessary before stent placement, because that is not always possible or conclusive and surgery is nonetheless indicated. If a second drainage procedure was indicated, both endoscopic and percutaneous approaches were possible at the discretion of the treatment team. Whenever a drainage procedure was performed elsewhere, we were unable to ensure if that procedure was performed according to the above guidelines.

Surgical procedure

After adequate biliary drainage, patients were considered for portal vein embolization (PVE) if the anticipated FLR was less than 40%. In all centers, neoadjuvant chemotherapy was not offered to patients. Surgery was performed by teams of experienced hepatobiliary surgeons. Restaging with cross-sectional imaging was performed whenever cross-sectional imaging was 4-6 weeks old. In the Aintree University Hospital Liverpool, staging laparoscopy was routinely performed before laparotomy in all patients. If, during the explorative laparotomy, peritoneal spread or unresectability were excluded, resection was performed. Intraoperative frozen sections

were examined routinely in all centers to rule out positive surgical resection margins at the central bile duct.

Definition of events

The primary outcome was stent failure after initial technically successful stent placement. This was defined as (1) cholangitis, defined as increased cholestasis, fever, and leukocytosis >10 × 10^9/L with need for admission with antibiotic treatment or reintervention, or (2) need for reintervention because of (1) insufficient biliary drainage, defined as the need to intervene to reduce bilirubin levels to <2 mg/dL (<34 mmol/L), or (2) endoscopic adverse events. Reinterventions were recorded until surgery, until the decision that surgery was not possible, or until death.

The secondary outcomes were the endoscopic adverse events as stated above, ability to undergo laparotomy, time to laparotomy, postoperative adverse events (consisting of infectious adverse events, bile leakage, benign hepaticojejunostomy stricture and posthepatectomy liver failure), and survival. Endoscopic adverse events were calculated per ERCP procedure and consisted of post-ERCP bleeding defined as hemoglobin drop of >3 g/dL requiring admission or reintervention, stent dislocation and migration (both distal and proximal) requiring reintervention, stent perforation of the duodenal wall, bile duct, or liver parenchyma requiring reintervention, and post-ERCP pancreatitis (PEP) according to the revised Atlanta criteria.[15] Time to subsequent laparotomy was defined as the number of days from initial endoscopic intervention until laparoscopy or explorative laparotomy. Outcomes were defined according to the International Study Group of Liver Surgery (ISGLS)[16,17] and graded according to the Clavien-Dindo classification.[18] R1 resection was defined as tumor cells within 1 mm of the resection margins at longitudinal and circumferential dissection planes. Survival was defined as the days from initial PBD or radical resection, up until death or loss to follow-up.

Statistical analysis

Outcomes were summarized by frequency and percentage for categoric and dichotomous variables, means and standard deviations for normally distributed continuous variables, and medians with interquartile ranges (IQRs) for continuous variables when not normally distributed. For statistical inference for categoric variables, chi-square test or Fisher exact test were used. For continuous variables, the unpaired *t* test or Mann-Whitney *U* test, depending on the distribution, was used. The Kaplan-Meier method was used to analyze overall survival. Survival curves were compared with the use of the log-rank test.

To adjust for confounders, propensity scores were estimated by using logistic model with predictors, including age, sex, diagnosis of primary sclerosing cholangitis (PSC), Bismuth-Corlette (BC) classification, World Health Organization (WHO) performance status, and American Society of Anesthesiologists (ASA) classification. Selection of predictors was based on the literature and expert opinions rather than statistical inference. With the use of the R package "matchit" and the propensity score matching (PSM) feature, each patient with SEMSs placement was paired to a patient with successful PS placement by means of the nearest-neighbor matching method, without replacement of patients and without using caliper. Patients with both SEMSs and PS placed at initial ERCP were included in the SEMSs group, to resemble clinical practice. Patients with missing data in one of the predictors were not included in the PSM cohort. We verified that covariates were balanced across the 2 groups by means of the statistical tests as stated above. Statistical analyses were performed with R version 4.1.1. Two-sided *P* values of <.05 were considered to be statistically significant.

RESULTS

Baseline characteristics of patients with resectable pCCA

In total, 504 patients with a high suspicion of resectable pCCA who underwent initial PBD with ERCP were included, as shown in Figure 1. Stent placement was successful in 474 (94%), and these patients were included in our study cohort. A SEMSs was placed at initial PBD in 61 patients (13%) and a PS in 413 (87%). In 47 patients (77%) the SEMSs was uncovered, and in 14 (23%) it was covered SEMSs. In 4 patients (7%), a PS was placed in addition to the SEMSs. In 22/413 patients (5%), the PS was replaced by SEMSs at reintervention, owing to inadequate drainage in 9 patients, cholangitis in 6, occlusion of the PS in 5, and elective exchange in 2. The results for the total study cohort, as well as all stent characteristics, are presented in Appendix 1 (available online at www.giejournal.org).

Propensity score matching

Propensity score matching (PSM) resulted in 59 patients each in the SEMSs and PS groups. Except for significantly less PVE performed in the SEMSs group, all baseline characteristics were similar between the groups. There was slight imbalance in the SMDs for age (SMD, 0.112), WHO performance status (SMD, 0.173), and BC type (SMD, 0.346). The baseline factors for the matched groups are presented in Table 1. The results for the matched cohort for initial stent type are presented below. The results for the matched cohort for eventual stent type (ie, patients with secondary SEMSs placement) are described in Appendix 1 (available online at www.giejournal.org).

Reintervention rate and adverse events

In the matched cohort of 118 patients, stent failure occurred significantly less in the SEMSs group (31% vs 64%; $P < .001$), as did cholangitis (15% vs 36%; $P = 0$) and re-ERCP (14% vs 54%; $P < .001$). Percutaneous trans-hepatic biliary drainage (PTBD) was not more often performed (9%

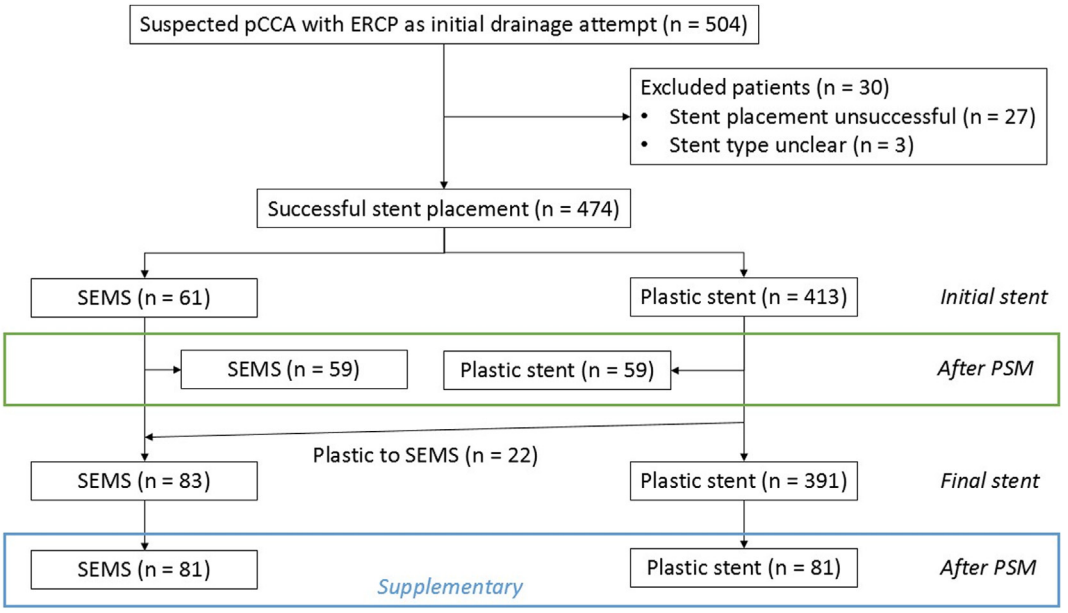

Figure 1. Flowchart of patient inclusion. pCCA, Perihilar cholangiocarcinoma; PSM, propensity score matching; SEMSs, self-expandable metal stent.

vs 7%; $P = 1$), as presented in Table 2. The location of first drainage was more often in a tertiary referral center for the SEMSs group than for the PS group (88% vs 58%; $P < .001$). Patients who underwent SEMSs placement underwent fewer ERCP procedures than patients with PS ($P < .001$), as presented in Table 2. These results were not significantly different from the unmatched cohort (Supplementary Table 2, available online at www.giejournal.org).

Adverse events per ERCP

A total of 171 ERCPs with stent placements were performed in the 118 matched patients. There were 69 SEMSs placements, of which 5 had PS placement during the same ERCP, and 102 PS placements. The PEP rate and stent migration difference were no longer significantly different compared with the unmatched results (Table 3; Supplementary Table 3, available online at www.giejournal.org).

Surgical procedures and outcomes

Of the 118 matched patients, 17 (14%) did not undergo surgical exploration, which did not differ between SEMSs and PS (19% vs 10%; $P = .19$). PBD with SEMSs, compared with PS, was not associated with a longer time to laparotomy (68 vs 59 days; $P = .084$). These results were not significantly different from the unmatched cohort (Supplementary Table 4, available online at www.giejournal.org).

Surgery. Surgical resection was performed in 27 (46%) of the 59 patients undergoing surgical exploration with SEMSs compared with 29 (49%) of the 59 with PS ($P = .712$) (Table 4). Overall, the type of resection did not differ between the 2 groups, but there was a tendency for more patients receiving extrahepatic bile duct resection without hepatectomy in favor of SEMSs (26% vs 17%) and extended hemihepatectomy in favor of SEMSs (48% vs 38%). SEMSs removal was easy and without adverse events in 26/27 patients (96%; 4 covered, 22 uncovered). In 1 patient, the two 10-cm (diameter unknown) ucSEMS had to be removed wire by wire, which took a longer time but was successful and without adverse events.

There were no significant differences in R1 resections (58% vs 59%; $P = .569$), benign disease (4% vs 0%; $P = .971$), postoperative adverse events according to Clavien-Dindo classification, or hepaticojejunostomy-associated adverse events, as presented in Table 5. There was a significant difference regarding postoperative liver failure according to the ISGLS criteria ($P = .016$) in favor of patients with PS despite similar preoperative bilirubin levels. In the unmatched cohort, this did not significantly differ between groups ($P = .178$).

Survival after stent placement and resection. Kaplan-Meier survival curves were constructed to analyze survival in the 2 stent groups based on initial stent placement and based on radical resection, as shown in Figures 2 and 3. After matching, the median overall survivals after initial stent placement were 15.9 months (95% CI, 11.2-26.0 months) in the SEMSs group and 14.2 months (95% CI, 8.7-29.1 months) in the PS group (log-rank $P = .81$). Survivals after radical resection were 23.0 months (95% CI, 13.2-51.1 months) for patients with SEMSs and 36.0 months (95% CI, 24.8-NA) for patients with PS (log-rank $P = .15$). In unmatched analysis, there was significantly longer survival in the PS group ($P = .044$).

TABLE 1. Baseline characteristics for the matched group

	Matched		
	SEMSs (n = 59)	PS n = 59)	*P* value
Age, y	68.08 (62.71-73.88)	68.78 (63.54-72.94)	.718
Male sex	34 (57.6)	34 (57.6)	1
ECOG/WHO performance status			.832
0	31 (52.5)	31 (52.5)	
1	15 (25.4)	18 (30.5)	
2	9 (15.3)	6 (10.2)	
3	4 (6.8)	4 (6.8)	
4			
ASA classification			1
1	7 (11.9)	7 (11.9)	
2	36 (61.0)	36 (61.0)	
3	16 (27.1)	16 (27.1)	
4	0	0	
PSC	0	0	1
CA19.9 at baseline (U/ml)*	92.00 (29.00-330.00)	246.00 (72.00-819.00)	.025
Total bilirubin at baseline (μmol/L)†	234.00 (142.00-320.00)	162.50 (93.25-276.00)	.070
Cholangitis before drainage	5 (8.5)	4 (6.8)	1
Bismuth-Corlette classification			.330
- 1	15 (25.4)	16 (27.1)	
- 2	12 (20.3)	5 (8.5)	
- 3A	10 (16.9)	12 (20.3)	
- 3B	22 (37.3)	26 (44.1)	
PVE	2 (3.4)	10 (16.9)	.033

Values are median (interquartile range) or n (%).
ASA, American Society of Anesthesiologists; *ECOG/WHO,* Eastern Cooperative Oncology Group/World Health Organization; *PS,* plastic stent; *PSC,* primary sclerosing cholangitis; *PVE,* portal vein embolization; *SEMSs,* self-expandable metal stent.
*Missing in 28 (23.7%).
†Missing in 15 (12.7%).

DISCUSSION

This study compared endoscopic PBD with the use of SEMSs or PS in a large cohort of patients with potentially resectable pCCA. After PSM, patients receiving SEMSs (with or without PS) had significantly less stent failure, cholangitis, and reintervention than patients receiving PS only. After surgical resection, postoperative outcomes and survival were similar except for significantly more severe postoperative liver failure in the SEMSs group.

We found significantly less stent failure in the SEMSs group compared with the PS group in the unmatched as well as the matched group. Data are scarce on this specific topic and only Grunhagen et al.[11] has previously described outcomes of both groups: There were no stent failures in the SEMSs group (n = 10), but in the 17 patients with PS, 7 stent failures occurred (41%). That study, however, did not include patients who did not undergo surgery owing to progressive disease or mortality. There are no other studies comparing SEMSs and PS in the preoperative setting for patients with pCCA. In the palliative setting, however, SEMSs have already proven their advantage.[19-21] A systematic review showed a lower occlusion and reintervention rate in the SEMSs group, but a similar 30-day mortality rate.[20] Another recent study found a significant lower risk of cholangitis and 6-month mortality in patients with bilateral SEMSs placement compared with multiple PS.[19] SEMSs have a wider lumen, which provides more rapid biliary decompression with lower rates of occlusion and a longer stent patency. This was also seen in our study, where significantly less cholangitis occurred after ERCP with SEMSs placement compared with PS. Even after including the patients with secondary SEMSs after initial PS, as reported in Appendix 1 (available online at www.giejournal.org), the results remained consistent. However, it is important to note that the majority of the SEMSs were placed at a tertiary

TABLE 2. Primary outcome and other biliary drainage procedure outcomes

	Matched		
	Metal (n = 59)	PS (n = 59)	*P* value
Stent failure	18 (30.5)	38 (64.4)	<.001
Cholangitis after stent	9 (15.3)	21 (35.6)	.02
Another ERCP after initial stent	8 (13.6)	32 (54.2)	<.001
PTBD after initial stent	5 (8.5)	4 (6.8)	1
First drainage at tertiary referral center	52 (88.1)*	34 (57.6)	<.001
Sphincterotomy†			<.001
Same ERCP	53 (94.6)	33 (67.3)	
Previous ERCP	1 (1.8)	3 (6.1)	
No	2 (3.6)	13 (26.5)	
Total no. of ERCPs			<.001
1	51 (86.4)	26 (44.1)	
2	7 (11.9)	18 (30.5)	
3	1 (1.7)	13 (22.0)	
4	0 (0.0)	2 (3.4)	

Values are n (%).
PTBD, percutaneous transhepatic biliary drainage.
*In the 7 patients with self-expandable metal stents (SEMSs) placed at a referral center, the stents were uncovered in 6 patients and covered in 1 patient.
†For plastic stents, missing in 10/59 (16.9%); for SEMSs, missing in 3/59 (5.1%). Rates calculated without taking into account missing variables.

referral center compared with only half of the PS. Also, not all choices for SEMSs placement compared with PS placement could be controlled for, such as potential blockage of side-branches. As reported in Appendix 1 (available online at www.giejournal.org), in the matched SEMSs group bilateral drainage was performed more often then in the PS group, potentially affecting this result. Suboptimal drainage with PS placed at nonacademic hospitals with less experience in these complex patients could be a reason for stent failure and indication for re-ERCP. Interestingly, the rate of sphincterotomy was higher in the SEMSs group than in the PS group.

Adverse events were similar in both groups after matching. In the unmatched cohort, significantly more PEP after SEMSs placement compared with PS placement was found (Table 3). A possible explanation for this might lie with some patient characteristics, because after matching it was no longer significantly different. In the matched cohort, 1 of the 2 patients with severe PEP did not receive a sphincterotomy. The dissimilarity was similar for stent migration. An important factor to note is that SEMSs placement does not jeopardize the proximal ducts as much in patients with BC type I and II pCCA, which characterized almost one-half of the SEMSs group. In patients with BC type III and IV pCCA, a combination of SEMSs and PS can be opted for as well.

Adverse events from stents, such as occlusion and subsequent cholangitis, can potentially postpone or preclude surgery. Grunhagen et al.[11] found a shorter time to laparotomy in patients with SEMSs compared with PS. In our unmatched and matched analysis, we were unable to validate these findings. This was primarily due to the different treatment strategies in the participating centers, because not all centers performed a separate staging laparoscopy before the planned liver resection. A laparoscopy procedure can potentially delay a resection procedure due to logistics and adverse events, but only if performed in a separate setting. PEP was not associated with a longer time to surgery. We found a similar percentage of patients undergoing any form of radical resection surgery, but after matching, survival was not different. This may be partially explained by the difference in treatment strategy regarding PVE, which was used more often in the PS group, besides more extended resections performed in the SEMSs group. Overall, analysis per center in the unmatched cohort did not show any significant differences regarding the rate of patients undergoing radical resection or timing to initial surgery (data not presented). The difference in postoperative liver failure could be attributed to differences in volume of the FLR, owing to more extended resections in the SEMSs group and less PVE, but unfortunately we did not have data on specific FLR volumes. In patients with up-front unilateral SEMSs who are eventually found to be unresectable, although the ucSEMS have proven their efficacy in the palliative setting, there could be some disadvantages with the undrained liver segments. However, recent research already show promising solutions in cases where additional drainage is indicated, such as stent-in-stent placement by means of ERCP and additional percutaneous ucSEMS placement.[22]

TABLE 3. Adverse events of ERCP procedures with a SEMSs or PS placement

	Matched		
	ERCP with SEMSs placement (n = 69)	ERCP with PS placement (n = 102)	*P* value
During procedure			
Displacement	0	0	1
Bleeding	1 (1.4)	1 (1.0)	–
Perforation	0	0	1
Sedation related	0	0	1
After procedure			
Post-ERCP pancreatitis	11 (15.9)	7 (6.9)	.06
Mild	7 (63.6)	3 (42.9)	
Moderate	2 (18.2)	4 (57.1)	
Severe	2 (18.2)*	0	
Stent migration	1 (1.4)	8 (7.8)	.09
Slight distal	1 (100)	4 (50.0)	
Complete distal	0	3 (37.5)	
Proximal	0	1 (12.5)	
Perforation after migration	0	0	1
Bleeding	1 (1.4)	2 (2.0)	1
Occlusion	7 (10.1)	18 (17.6)	.17
Cholangitis	10 (14.5)	32 (31.4)	.012
Death	2 (2.9)	1 (1.0)	.57

Values are n (%). ERCP procedures without SEMSs or PS placement are excluded from this table, because it was possible for patients to undergo an unsuccessful ERCP or reintervention without stent placement.
PS, plastic stent; *SEMSs,* self-expandable metal stent.
*In 1 of the 2 patients with severe post-ERCP pancreatitis, no sphincterotomy was performed.

TABLE 4. All patients who had at least 1 surgical procedure

	Matched		
	SEMSs (n = 48)	PS (n = 53)	*P* value
Time to surgery from first stent, d	52.00 (34.00-71.00)	47.00 (29.50-81.75)	.870
Time to laparotomy from first stent, d	68.00 (54.00-92.00)	59.00 (43.25-84.00)	.084
First surgical procedure			.003
Radical resection	5 (10.4)	18 (34.0)	
Staging laparoscopy	38 (79.2)	25 (47.2)	
Explorative laparotomy	5 (10.4)	10 (18.9)	
Explorative laparotomy	11 (22.9)	14 (26.4)	.860
Staging laparoscopy	39 (81.2)	25 (47.2)	<.001
Radical resection	27 (56.2)	29 (54.7)	1

Values are median (interquartile range) or n (%).
PS, Plastic stent; *SEMSs,* self-expandable metal stent.

SEMSs removal was not an issue in this series. This finding is in line with other, albeit very small, studies showing low rates of difficult SEMSs removal.[12-14] Two out of 15 patients included in those studies had to undergo wire-by-wire removal, which was successful and uneventful in both.[13]

Another factor up for debate is the method of PBD. The recently published INTERCPT trial was the second randomized controlled trial that compared endoscopic versus percutaneous PBD in patients with resectable pCCA.[23,24] Unfortunately, both trials were terminated early. Arguably, some patients may be best served by up-front percutaneous biliary drainage. PBD with ERCP is limited by the difficulty and unpredictability on whether a stent is placed in the correct segment, as well as that only segments in which contrast

TABLE 5. Outcomes of radical resections

	Matched		
	SEMSs (n = 27)	PS (n = 29)	*P* value
Staging laparoscopy before radical resection	22 (81.5)	11 (37.9)	.002
Explorative laparotomy before radical resection	0 (0.0)	0 (0.0)	–
Total bilirubin before surgery (μmol/L)	16.00 (9.50-25.50)	17.50 (14.00-33.50)	.092
Resection type			.550
Bile duct resection	7 (25.9)	5 (17.2)	
Hilum	0 (0.0)	0 (0.0)	
Left hemihepatectomy	4 (14.8)	6 (20.7)	
Left extended hemihepatectomy	5 (18.5)	6 (20.7)	
Liver transplantation	0 (0.0)	0 (0.0)	
Right hemihepatectomy	3 (11.1)	7 (24.1)	
Right extended hemihepatectomy	8 (29.6)	5 (17.2)	
Additional pancreatoduodenectomy	0 (0.0)	1 (3.4)	1.000
Frozen section proximal = positive	0 (0.0)	0 (0.0)	–
Frozen section distal = positive	0 (0.0)	4 (13.8)	.138
Radicality			.569
R0	11 (42.3)	10 (34.5)	
R1	15 (57.7)	17 (58.6)	
R2	0 (0.0)	1 (3.4)	
Missing	0 (0.0)	1 (3.4)	
Benign disease	1 (3.7)†	0 (0.0)	.971
Clavien-Dindo classification			.227
<3	16 (59.3)	15 (51.7)	
3A	4 (14.8)	6 (20.7)	
3B	2 (7.4)	2 (6.9)	
4A	0 (0.0)	4 (13.8)	
4B	0 (0.0)	0 (0.0)	
5	5 (18.5)	2 (6.9)	
Postoperative liver failure*			.016
1	22 (81.5)	26 (89.7)	
2	0 (0.0)	3 (10.3)	
3	5 (18.5)	0 (0.0)	
HJ leak	1 (3.7)	4 (13.8)	.393
Benign HJ stricture	4 (14.8)	6 (20.7)	.822
90-day mortality	6 (22.2)	2 (6.9)	.209

Values are n (%) or median (interquartile range).
HJ, Hepaticojejunostomy; *PS,* plastic stent; *SEMSs,* self-expandable metal stent.
*According to the International Study Group of Liver Surgery criteria.
†IgG4-mediated disease. Patient received an fully covered SEMSs at initial endoscopic retrograde cholangiopancreatography.

injection was successful can be drained. Even in the setting of a randomized controlled trial with expert treatment centers, the adverse event rates for endoscopic and percutaneous PBD were 67% and 75%, respectively. Owing to these adverse events, overall survival of these patients is limited, and only radical resection gives them a chance of longer overall survival. Therefore, there is a strong need to improve PBD methods to reduce PBD-related adverse events and increase the number of patients undergoing radical resection. This also stresses the need for adequate imaging before drainage procedures and a multidisciplinary approach to optimize the drainage strategy.

The primary strengths of this study are the large number of patients included and the method of patient selection, focusing on all potentially resectable pCCA patients, because this gives us information about preoperative biliary adverse

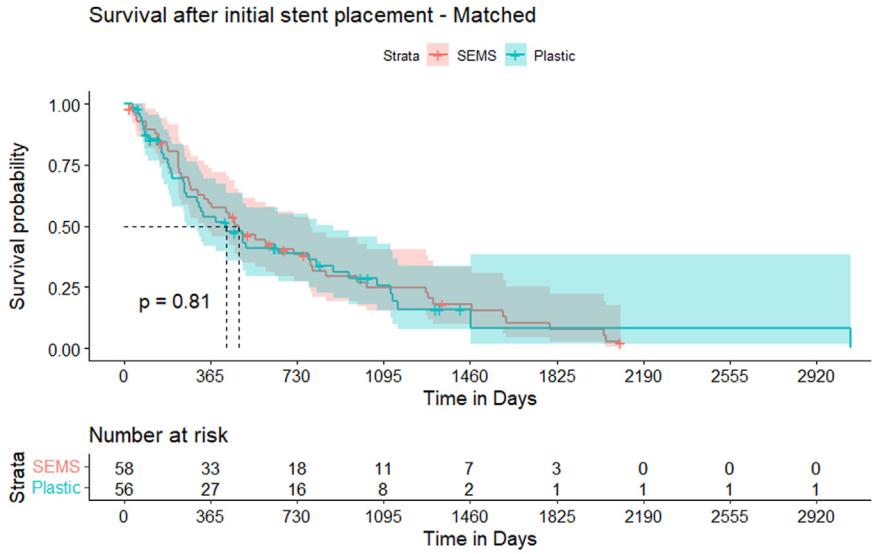

Figure 2. Kaplan-Meier curve for survival after ERCP with successful initial stent placement—for matched results. In the matched cohort, median survival was 482 days (95% CI, 338-787 days) for the SEMSs group and 429 days (95% CI, 263-881 days) for the PS group. *P* value is according to the log-rank test. SEMSs, Self-expandable metal stent.

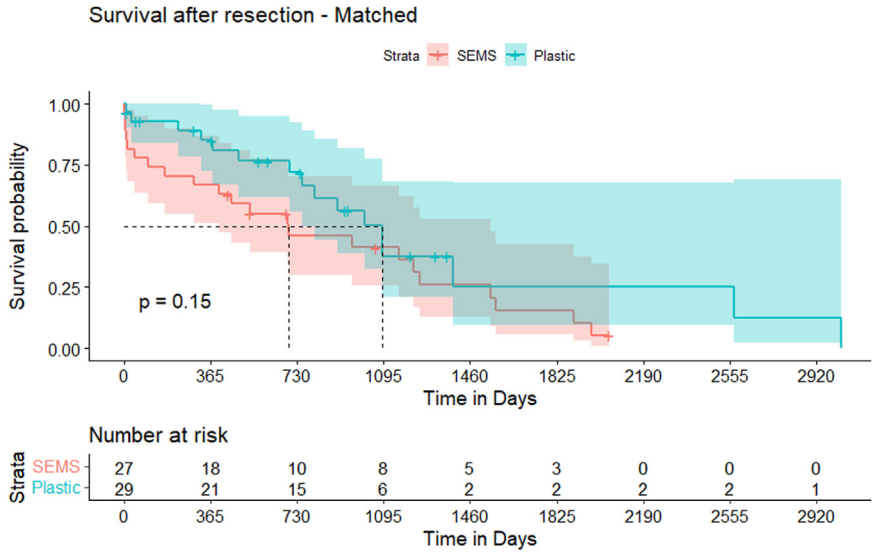

Figure 3. Kaplan-Meier curve for survival after radical resection—for matched results. In the matched cohort, median survival was 695 days (95% CI, 400-1545 days) for the SEMSs group and 1088 days (95% CI, 751-NA days) for the PS group. *P* value is according to the log-rank test. SEMSs, Self-expandable metal stent.

events and disease progressions. Moreover, we used PSM to adjust for the most important potential confounders, thereby strengthening our findings. Also, by reporting both unmatched and matched results, insight is given on the fundamental differences between these groups and how this may influence the results in our sensitivity analysis in Appendix 1 (available online at www.giejournal.org). However, the following limitations should be mentioned. First, the retrospective design has inherent biases, such as selection bias. We included all potentially resectable pCCAs from prospectively collected databases on pCCA that underwent an ERCP as initial method to obtain PBD and performed matching to make the 2 groups more comparable. Second, information bias is an issue because certain variables had missing data, such as ASA classification and WHO performance status; this was not, however, different for the 2 treatment groups. Matching was performed only with complete cases, thereby reducing the included patients significantly. Moreover, it was impossible to use specific data on stent or drainage characteristics owing to the retrospective design, as well as

information about the appearance of the proximal bile duct diameter, and antibiotic and nonsteroidal antiinflammatory drug usage. Therefore, univariable and multivariable analyses to look at other potentially important confounding factors was not possible. Third, the indication for SEMSs placement in centers other than the Aintree University Hospital were different. An SEMSs could already have been placed at the referring center for unresectable pCCA but the pCCA turns out to be resectable instead. Not all factors for stent type choice could be controlled for, possibly resulting in a more difficult to treat PS group. Finally, the fact that almost all SEMSs patients came from 1 tertiary referral center can limit the generalizability of this study's findings.

PBD with SEMSs shows promising results in patients without PSC and BC types I to III. Despite potential benefits of this strategy, removable PS remain a very practical initial stent choice. Some important considerations are (1) cytopathologic diagnosis, which can be complicated by ucSEMS placement, (2) indeterminate biliary strictures mimicking pCCA, in which ucSEMS placement would be harmful, (3) other factors such as duration of the obstruction and underlying liver function that may impair stent function, (4) costs of SEMSs, which are significantly higher than PS, and (5) SEMSs availability at treatment centers. To study this and change current practice, multicenter randomized controlled trials with a clear treatment strategy and end points should be performed. Patients with high suspicion of resectable pCCA should be randomized to direct SEMSs or PS placement. Adequate cross-sectional imaging should be performed earlier, because interpretation of magnetic resonance imaging and computed tomography is hampered with stents in situ. More importantly, ucSEMS should be placed only when the pCCA diagnosis is very likely after consultation with an experienced multidisciplinary team. Whenever the endoscopist is unsure about the diagnosis, potential stent function, or life expectancy, or whenever individual anatomy may not be suitable for ucSEMS, PS should be placed instead. Obtaining cytopathologic proof is important, but the decision to perform surgery should be made earlier in the light of limited accuracy of the current available methods. PVE and laparoscopy should be performed to improve the treatment pathway, increasing the number of patients eligible for resection and sparing unresectable patients a more invasive laparotomy. An upcoming pilot study on ucSEMS placement by ERCP as PBD (International Clinical trials Registry Platform: NL9600) should start further exploration of this promising technique.

DISCLOSURE

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Abbreviations: BC, Bismuth-Corlette; FLR, future liver remnant; PBD, preoperative biliary drainage; pCCA, peribilar cholangiocarcinoma; PEP, post-ERCP pancreatitis; PS, plastic stent; PSC, primary sclerosing cholangitis; PSM, propensity score matching; PVE, portal vein embolization; SEMSs, self-expandable metal stent; ucSEMS, uncovered self-expandable metal stents.

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APPENDIX 1

Abbreviations: ASA, American Society of Anesthesiologists; BC, Bismuth-Corlette; ECOG, Eastern Cooperative Oncology Group; ERCP, endoscopic retrograde cholangiopancreatography; fcSEMS, fully covered SEMSs; PBD, preoperative biliary drainage; pCCA, perihilar cholangiocarcinoma; PS, plastic stent; PSC, primary sclerosing cholangitis; PTBD, percutaneous transhepatic biliary drainage; PVE, portal vein embolization; SEMSs, self-expandable metal stent; SMD, standardized mean difference; ucSEMS, uncovered SEMSs; WHO, World Health Organization

Stents placed per center

	SEMSs	PS
Liverpool	53	65
Amsterdam	6	179
Rotterdam	2	137
Innsbruck	0	32
Total	61	413

Fourteen (30%) of the SEMSs were coated/covered, and the remaining 47 were uncovered. With 4 (7%) or the 61 SEMSs, in addition to the SEMSs, a plastic stent was placed at initial ERCP. All of those 4 patients were included in the matched analysis.

Stent characteristics

	ucSEMS	fcSEMS	PS
Total no. of stents placed	91	26	959
Length, cm			
4	1 (1.1)	1 (3.8)	–
5	–	–	3 (0.3)
6	4 (4.4)	5 (19.2)	1 (0.1)
7	–	–	16 (1.7)
8	31 (34.1)	10 (38.5)	4 (0.4)
9	–	–	48 (5.0)
10	47 (51.6)	10 (38.5)	31 (3.2)
11	–	–	17 (1.8)
12	–	–	257 (26.8)
12.5	–	–	1 (0.1)
13	–	–	47 (4.9)
13.5	–	–	1 (0.1)
14	1 (1.1)	–	61 (6.4)
15	–	–	265 (27.6)
16	–	–	9 (0.9)
17	–	–	17 (1.8)
18	–	–	54 (5.6)
19	–	–	20 (2.1)
20	–	–	4 (0.4)
Missing	7 (7.7)	–	103 (10.7)
Diameter, mm (SEMSs) or F (PS)			
4	–	–	1 (0.1)
5	–	–	3 (0.3)
6	–	2 (7.7)	–
7	–	–	200 (20.9)
8	30 (33)	6 (23.1)	2 (0.2)
8.5	2 (2.2)	–	8 (0.8)
9	–	–	2 (0.2)
10	47 (51.6)	15 (57.7)	628 (65.5)
12	–	–	1 (0.1)
14	–	–	1 (0.1)
Missing	12 (13.3)	3 (11.5)	113 (11.8)
Crossing papilla			
Yes	73 (80.2)	25 (96.2)	959 (100)
No	6 (6.6)	1 (3.8)	–
Missing	12 (13.2)	0	

Values are n (%). The number of stents placed differs from the total number of ERCPs with that specific stent because multiple stents can be placed in one ERCP. In 16 placed stents, all characteristics were missing, including 1 stent described as "metal" but unclear about what type of SEMSs.

Stent characteristics at initial ERCP in matched cohort

	SEMSs (n = 59)	PS (n = 59)
No. of stents placed at index ERCP		
1	39 (66.1)	54 (91.5)
2	20* (33.9)	5 (8.5)
Bilateral drainage	16 (27.6†)	5 (8.5)

Values are n (%).
*In 4 patients, the second stent was PS.
†Unknown in 1 patient: rate calculated as 16 out of 58.

SENSITIVITY ANALYSIS I: COMPLETE COHORT

These supplementary results describe the results of the baseline characteristics of the total study cohort with unmatched data.

Baseline characteristics of patients with resectable pCCA

Stent placement was successful in 474 (94%), and those patients were included in our study cohort. An SEMSs was placed at initial PBD in 61 patients (13%) and a PS in 413 (87%). The SEMSs was uncovered in 47 patients (77%) and covered in 14 (23%). In 4 patients (7%) a PS was placed in addition to the SEMSs. Supplementary Table 1 presents the patient and disease characteristics of the 2 groups with SEMSs or PS of the total unmatched cohort.

Reintervention rate and adverse events

In the unmatched cohort, stent failure occurred significantly less in the SEMSs group (31% vs 66%; $P < 0.001$), as did cholangitis (15% vs 33%; $P < .001$), re-ERCP (13% vs 53%; $P < .001$), and PTBD (10% vs 13%; $P = 0.61$). Patients who received initial SEMSs underwent significantly fewer ERCP procedures than patients with plastic stents ($P < 0.001$). Results are presented in Supplementary Table 2. Supplementary Figure 1 shows the survival after initial ERCP.

Adverse events per ERCP

A total of 820 ERCPs with stent placements were performed in 474 patients. There were 86 SEMSs placements, of which 8 had plastic stent placement during the same ERCP, and 734 plastic stent placements. Post-ERCP pancreatitis occurred significantly more often after SEMSs placement (15% vs 8%; $P = .02$). Stent migration occurred significantly less after SEMSs placement compared with PS (2% vs 15%; $P = .001$). Cholangitis after SEMSs placement compared with plastic stents was lower: 15% compared with 32% ($P = .001$). Results are presented in Supplementary Table 3.

Surgical procedures and outcomes

Of the 474 unmatched patients, 77 (16%) did not undergo surgical exploration, which did not differ between the 2 treatment groups (18% vs 16%; $P = .685$). The results of all surgical procedures and outcomes are presented in Supplementary Tables 4 and 5.

Surgical resection was performed in 29 (48%) of the 61 patients undergoing surgical exploration with SEMSs and in 209 (51%) of the 413 patients with plastic stents ($P = .655$). Overall, the type of resection did not differ between the 2 groups. SEMSs removal was easy and without adverse events in almost all patients. In the patient without easy removal, SEMSs had to be removed wire-by-wire, which took a longer time, although it was successful and without adverse events.

There were no differences in R1 resections (57% vs 49%; $P = 0.75$), benign disease (3% vs 7%; $P = .601$), postoperative adverse events according to Clavien-Dindo classification ($P = .209$), or postoperative liver failure according to the ISGLS criteria ($P = .178$). Hepaticojejunostomy leakage diagnosis and benign hepaticojejunostomy stricture formation were similar in the 2 groups (10% vs 19% [$P = .37$] and (14% vs 11% [$P = .896$], respectively). Supplementary Figure 2 shows the survival after radical resection for both groups.

SENSITIVITY ANALYSIS II: EVENTUAL STENT TYPE

These supplementary results describe the results of the baseline characteristics of the total study cohort with unmatched data and subsequently of the matched groups of eventual stent type (ie, patients with secondary SEMSs placement).

Baseline characteristics of patients with pCCA (eventual stent type)

A total of 413 patients (87%) received PS, but in 22 patients (5%) they were replaced by SEMSs at reintervention. Those 22 patients had their PS replaced by SEMSs because of inadequate drainage in 9 patients, cholangitis in 6, occlusion of the PS in 5, and elective exchange in 2. Finally, a total of 83 patients (19%) with SEMSs and 391 (85%) with PS were included. Baseline characteristics were similar in the 2 groups. Type of BC classification was different, however, with BC type IV more common in the PS group. An important difference was the use of PVE, which was performed significantly less in patients with SEMSs (10% vs 21%; $P = .025$). In addition, SEMSs were used less often in patients with PSC (1% vs 7%; $P = .071$).

Propensity score matching

To adjust for differences in baseline characteristics and possible confounders, a 1:1 PSM was performed on eventual stent type. A total of 81 patients in the SEMSs group were matched with 81 patients in the PS group. Following matching, there were no significant differences in baseline characteristics between the 2 groups, although there was slight imbalance in the SMDs for age (SMD, 0.107), WHO performance score (SMD, 0.103), ASA classification (SMD, 0.153), and BC classification (SMD, 0.122).

Reintervention rate and adverse events

In the matched cohort, stent failure occurred significantly less in the SEMSs group (28% vs 67%; $P < .001$), as did cholangitis (15% vs 36%; $P = .002$), re-ERCP (11% vs 46%; $P < .001$), and PTBD (11% vs 20%; $P = .13$). The stent failure was calculated from the SEMSs placement, not initial stent placement. After matching, patients who underwent SEMSs placement no longer underwent fewer ERCP procedures than patients with PS ($P = .153$).

Adverse events per ERCP

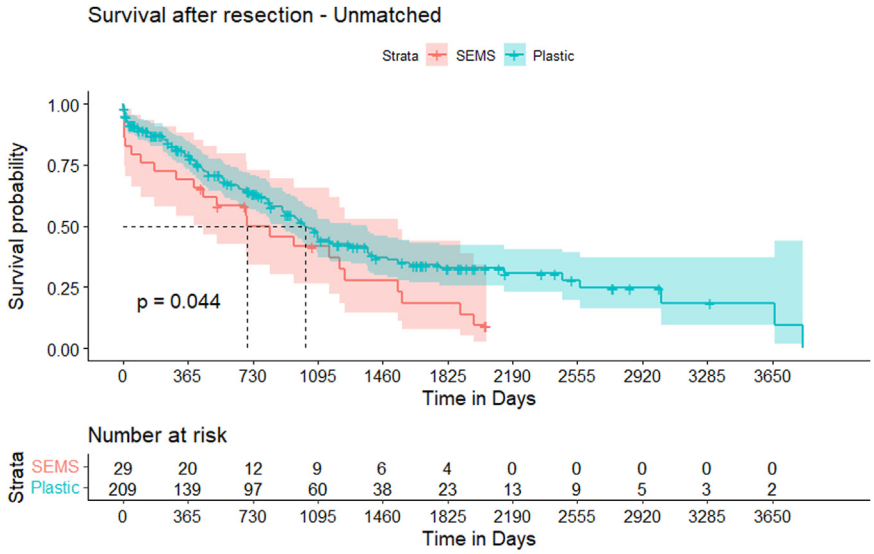
A total of 240 ERCPs with stent placements were performed in the 162 matched patients. There were 84 SEMSs placements, of which 8 had PS placement during the same ERCP, and 156 PS placements. The post-ERCP pancreatitis rate and stent migration difference were not significantly different. Cholangitis after SEMSs placement compared with PS was lower, 16% compared to 31% ($P = .009$).

Surgical procedures and outcomes

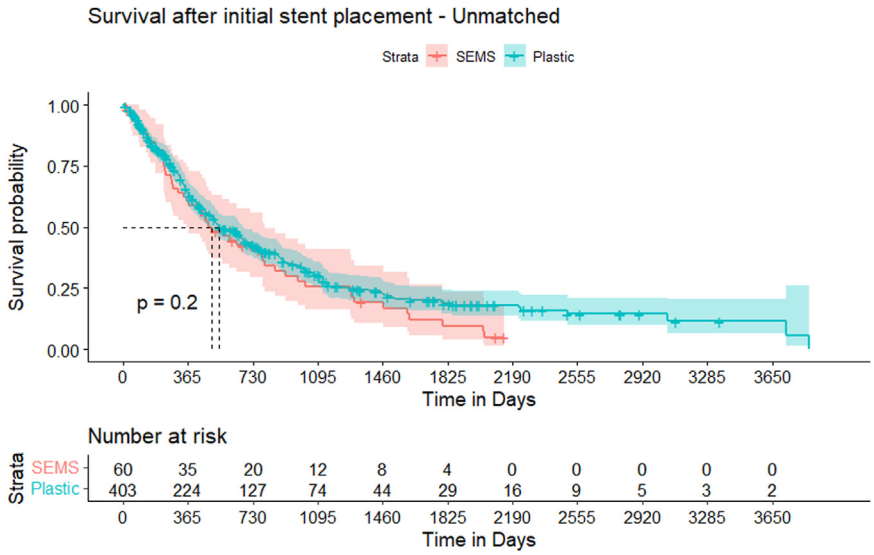
Of the 162 matched patients, 23 (14%) did not undergo surgical exploration, which did not differ between the 2 treatment groups (16% vs 12%; $P = .653$).

Surgical resection was performed in 39 (57%) of the 68 patients undergoing surgical exploration with SEMSs versus 42 (59%) of the 71 patients with PS ($P = .965$). Overall, the type of resection did not differ between the 2 groups, but there were more patients receiving bile duct resection with SEMSs (10% vs 26%) and left hemihepatectomy with PS (13% vs 24%). SEMSs removal was easy and without adverse events in 38 (97%) out of the 39 patients. In the patient without easy removal, SEMSs had to be removed wire-by-wire, which took a longer time, although it was successful and without adverse events.

There were no differences in R1 resections (55% vs 48%; $P = 0.646$), benign disease (3% vs 0%; $P = .97$), postoperative adverse events according to Clavien-Dindo classification ($P = .254$), or postoperative liver failure according to the ISGLS criteria ($P = .261$). There were significantly fewer hepaticojejunostomy leakage diagnoses in the SEMSs group (5% vs 21%; $P = .049$) and similar benign hepaticojejunostomy stricture formation (8% vs 10%; $P = 1$). Median overall survivals were 23 months (95% CI, 13-51 months) in the SEMSs group and 30 months (95% CI, 19-NA months) in the PS group (log-rank $P = .59$).



Supplementary Figure 1. Kaplan-Meier curves for survival after ERCP with successful initial stent placement. Median survival in the unmatched cohort was 498 days (95% CI, 356-796 days) for the SEMSs group and 538 days (95% CI, 494-677 days) for the PS group. 11 patients were excluded from survival analysis because of unknown stent placement date or no clear follow-up date.



Supplementary Figure 2. Kaplan-Meier curves for survival after radical resection. Median survival after radical resection in the unmatched cohort was 695 days (95% CI, 453-1545 days) for the SEMSs group and 1023 days (95% CI, 899-1373 days) for the PS group.

SUPPLEMENTARY TABLE 1. Baseline characteristics for the unmatched group

	Unmatched		
	SEMSs (n = 61)	PS (n = 413)	*P* value
Age, y[1]	68.08 (62.52-74.08)	67.11 (58.65-73.10)	.111
Male sex	35 (57.4)	255 (61.7)	.608
ECOG/WHO performance status[2]			.163
0	31 (50.8)	208 (51.9)	
1	16 (26.2)	138 (34.4)	
2	10 (16.4)	46 (11.5)	
3	4 (6.6)	8 (2.0)	
4	0 (0.0)	1 (0.2)	
ASA classification[3]			.66
1	7 (11.7)	69 (17.2)	
2	37 (61.7)	241 (60.2)	
3	16 (26.7)	89 (22.2)	
4	0 (0.0)	1 (0.2)	
PSC	0 (0.0)	29 (7.0)	.064
CA19.9 at baseline (U/ml)[4]	98.00 (30.75-325.50)	214.00 (62.25-884.25)	.005
Total bilirubin at baseline (μmol/L)[5]	230.00 (134.00-314.00)	165.11 (88.00-282.75)	.029
Cholangitis before drainage[6]	5 (8.2)	47 (11.5)	.589
Bismuth-Corlette classification[7]			<.001
1	15 (25.0)	43 (10.5)	
2	12 (20.0)	63 (15.4)	
3A	11 (18.3)	140 (34.3)	
3B	22 (36.7)	68 (16.7)	
4	0 (0.0)	94 (23.0)	
PVE	4 (6.6)	86 (20.8)	.013

Values are median (interquartile range) or n (%).
[1]Missing in 1 (0.2%).
[2]Missing in 12 (2.5%).
[3]Missing in 14 (3%).
[4]Missing in 124 (26.2%).
[5]Missing in 67 (14.1%).
[6]Missing in 3 (0.6%).
[7]Missing in 6 (1.3%).

SUPPLEMENTARY TABLE 2. Primary outcome and other biliary drainage procedure outcomes

	Unmatched		
	SEMSs (n = 61)	**PS (n = 413)**	***P* value**
Stent failure	19 (31.1)	274 (66.3)	<.001
Cholangitis after stent	9 (14.8)	138 (33.4)	<.001
Another ERCP after initial stent	8 (13.1)	217 (52.5)	<.001
PTBD after initial stent	6 (9.8)	54 (13.1)	.614
First drainage at tertiary referral center	52 (85.2)	227 (55.0)	<.001
Sphincterotomy*			.016
Same ERCP	54 (93.1)	248 (73.5)	
Previous ERCP	2 (3.4)	35 (10.8)	
No	2 (3.4)	41 (12.7)	
Total no. of ERCPs			<0001
1	52 (85.2%)	178 (43.1%)	
2	7 (11.5%)	128 (31.0%)	
3	2 (3.3%)	66 (16%)	
4	–	29 (7.0%)	
5	–	6 (1.5%)	
6	–	1 (0.2%)	
7	–	2 (0.5%)	
8	–	2 (0.5%)	
9	–	1 (0.2%)	

Values are n (%).
*For SEMSs, missing in 3/61 (4.9%); for PS, missing in 89/413 (21.5%). Rates calculated for nonmissing: out of 58 for SEMSs and out of 324 for PS.

SUPPLEMENTARY TABLE 3. Adverse events of ERCP procedures with SEMSs or PS placement

	Unmatched		
	ERCP with SEMSs placement (n = 86)	ERCP with PS placement (n = 734)	*P* value
During procedure			
Displacement	0	6 (0.8)	1
Bleeding	1 (1.2)	9 (1.2)	1
Perforation	0	5 (0.7)	1
Sedation related	0	2 (0.3)	1
After procedure			
Post-ERCP pancreatitis	13 (15.1)	56 (7.6)	.02
Mild	9 (69.2)	41 (67.9)	
Moderate	2 (15.4)	13 (23.2)	
Severe	2 (15.4)	2 (3.6)	
Stent migration	2 (2.3)	109 (14.9)*	.001
Slight distal	1 (50.0)	53 (48.6)	
Complete distal	1 (50.0)	34 (31.2)	
Proximal	0	15 (13.8)	
Perforation after migration	0	4 (3.7)†	1
Bleeding	1 (1.2)	8 (1.1)	1
Occlusion	8 (9.3)	79 (10.8)	.17
Cholangitis	13 (15.1)	235 (32.0)	.001
Death	2 (2.3)	7 (1.0)	.24

Values are n (%). ERCP procedures without SEMSs or PS placement are excluded from this table, because it was possible for patients to undergo an unsuccessful ERCP or reintervention without stent placement.
*In 1 patient, complete distal together with proximal stent migration; in 6 patients, migration direction was unclear.
†In 1 patient, perforation of the liver parenchyma occurred after proximal migration; in 3 patients, perforation of the opposing duodenal wall occurred after distal migration.

SUPPLEMENTARY TABLE 4. All patients who had at least 1 surgical procedure

	Unmatched		
	SEMSs (n = 50)	PS (n = 357)	*P* value
Time to surgery from first stent, d	50.00 (33.00-70.00)	56.00 (37.00-81.00)	.191
Time to laparotomy from first stent, d	68.00 (54.00-98.50)	66.00 (46.00-98.00)	.276
First surgical procedure			<.001
Radical resection	5 (10.0)	124 (34.7)	
Staging laparoscopy	40 (80.0)	143 (40.1)	
Explorative laparotomy	5 (10.0)	90 (25.2)	
Explorative laparotomy	11 (22.0)	116 (32.5)	.181
Staging laparoscopy	41 (82.0)	145 (40.6)	<.001
Radical resection	29 (58.0)	209 (58.5)	1

Values are n (%).

SUPPLEMENTARY TABLE 5. Outcomes of radical resections

	Unmatched		
	SEMSs (n = 29)	**PS (n = 209)**	***P* value**
Staging laparoscopy before radical resection	24 (82.8)	78 (37.3)	<.001
Explorative laparotomy before radical resection	0 (0.0)	7 (3.3)	.679
Total bilirubin before surgery (μmol/L)	14.50 (9.75-24.75)	16.00 (10.00-32.00)	.275
Resection type			.51
Bile duct resection	7 (24.1)	33 (15.8)	
Hilum	0 (0.0)	5 (2.4)	
Left hemihepatectomy	4 (13.8)	40 (19.1)	
Left extended hemihepatectomy	5 (17.2)	21 (10.0)	
Liver transplantation	0 (0.0)	7 (3.3)	
Right hemihepatectomy	4 (13.8)	46 (22.0)	
Right extended hemihepatectomy	9 (31.0)	57 (27.3)	
Additional pancreatoduodenectomy	0 (0.0)	11 (5.3)	.369
Frozen section proximal = positive	0 (0.0)	10 (4.8)	.478
Frozen section distal = positive	0 (0.0)	15 (7.2)	.279
Radicality			.75
- R0	11 (39.3)	96 (48.7)	
- R1	16 (57.1)	96 (48.7)	
- R2	0 (0.0)	1 (0.5)	
- Missing	1 (3.6)	4 (2.0)	
Benign disease	1 (3.4)	15 (7.2)	.601
Clavien-Dindo classification			.209
<3	16 (55.2)	94 (45.0)	
3A	5 (17.2)	58 (27.8)	
3B	2 (6.9)	18 (8.6)	
4A	0 (0.0)	18 (8.6)	
4B	1 (3.4)	2 (1.0)	
5	5 (17.2)	19 (9.1)	
Postoperative liver failure*			.178
1	0 (0.0)	9 (4.3)	
2	0 (0.0)	4 (1.9)	
3	5 (17.2)	15 (7.2)	
HJ leak	3 (10.3)	40 (19.1)	.37
Benign HJ stricture	4 (13.8)	23 (11.0)	.896
90 day mortality	6 (20.7)	22 (10.5)	.199

Values are n (%) or median (interquartile range).
*According to the International Study Group of Liver Surgery criteria.